CLINICAL STUDY MER-XMT-1536-1 (UPLIFT Cohort)

SUMMARY ATTACHMENT

DATE: 11 June 2024

The purpose of this document is to post result-related information via a summary attachment for the MER-XMT-1536-1 clinical study, UPLIFT Cohort.

Reference is made to the press release dated July 27th, 2023, in which Mersana announced that the UPLIFT clinical trial of XMT-1536 in platinum-resistant ovarian cancer did not meet its primary endpoint and that the Sponsor was discontinuing further development of XMT-1536.

UPLIFT, within study MER-XMT-1536-1 (EUDRACT 2020-000630-17), was a single-arm clinical trial that enrolled platinum-resistant ovarian cancer patients with one to four prior treatment regimens. The primary endpoint for UPLIFT was the investigator-assessed objective response rate (ORR) in the NaPi2b-positive population (defined by a tumor proportion score (TPS) of ≥75%). Based on the May 31, 2023, data cutoff date, the ORR by investigator was 15.6% (10.0%, 22.7%) in the NaPi2b-positive population (n=141); the lower bound of the confidence interval for the primary endpoint did not meet the goal of excluding a 12% ORR seen with standard-of-care single-agent chemotherapy.

Based on the results of the primary analysis of UPLIFT, the Sponsor decided to terminate the XMT-1536 clinical development program.

At the time of this decision, only participants who were then ongoing in the UPLIFT Cohort, who were deriving sufficient clinical benefit relative to risk from XMT-1536, as determined by the Investigator, were allowed to remain ongoing and continue receiving XMT-1536.

The Sponsor has finalized the Clinical Study Report, which contains data based on the primary completion date of May 31st, 2023 and no other analyses are planned for the UPLIFT cohort within study MER-XMT-1536-1.

In accordance with the *Commission Guideline — Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 (Section 4.3 Timing),* since result related data are publicly available based on the primary completion date of May 31st, 2023, the Sponsor is providing below the Clinical Study Report synopsis with partial results, before the end of the trial.

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1. SYNOPTIC SUMMARY

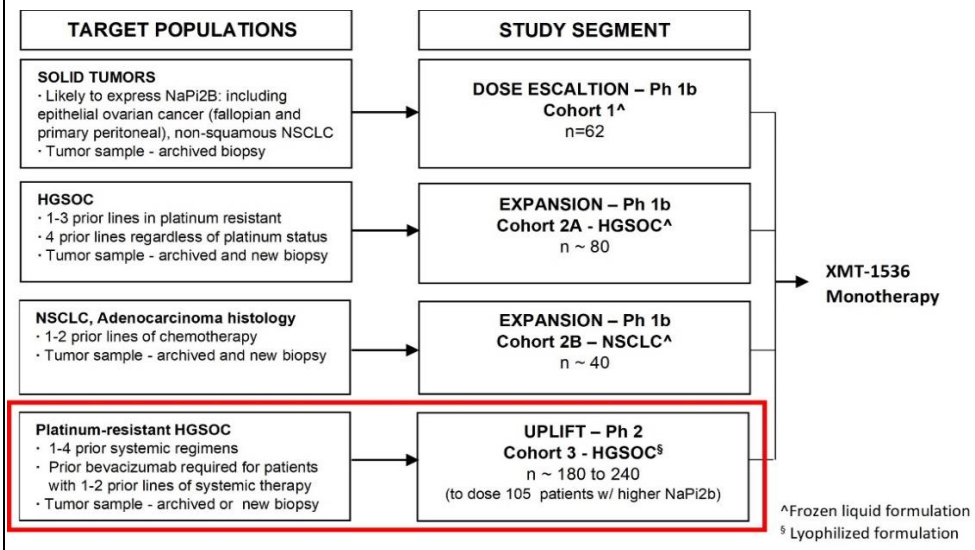
Name of Sponsor/Company: Mersana Therapeutics, Inc.	
Name of Investigational Product: Upifitamab rilsodotin (XMT-1536)	**Name of Active Ingredient:** XMT-1536 Antibody-drug conjugate
Title of Study: A Phase 1b/2, First-in-Human, Dose Escalation and Expansion Study of XMT-1536 in Patients with Solid Tumors Likely to Express NaPi2b	
Study Number: MER-XMT-1536-1 (UPLIFT) Cohort	
Study Phase: 1b/2	
Study Initiation Date:	03 October 2022 (date the first participant was randomized)
Primary Completion Date:	29 September 2023 (last participant last visit following primary analysis) 09 October 2023 (date of database lock)
Report Date:	11 June 2024

Study Design and Methodology:

UPLIFT was Cohort 3 of Study MER-XMT1536-1, A Phase 1b/2, First-in-Human, Dose Escalation and Expansion Study of XMT-1536 In Patients with Solid Tumors Likely to Express NaPi2b. It was conducted as an open label, multicenter study to evaluate the safety, pharmacokinetics, and efficacy of upifitamab rilsodotin monotherapy at the recommended phase 2 dose in participants with platinum-resistant high-grade serous ovarian cancer (HGSOC) including fallopian tube and primary peritoneal cancer; the study schema is presented below.

Participants enrolled in the study were screened, treated, monitored, and assessed at regular intervals while receiving treatment and followed-up after treatment discontinuation.

Figure 1: MER-XMT-1536-1 Overall Study Design Schema



Abbreviations: EXP=Expansion; HGSOC=high-grade serous ovarian cancer; NaPi2b=type II sodium dependent phosphate transporter (*SLC34A2*); NSCLC=non-small cell lung cancer; Ph=Phase.

Objectives and Endpoints (UPLIFT Segment):

Key Endpoint	Definition of populations and sample size
Primary Endpoint	
Confirmed investigator-assessed Objective Response Rate (ORR) in the ITT-NaPi2b Positive (TPS≥75) population at a starting dose of 36 mg/m^2 q4w (capped at a BSA of 2.2 m^2)	ITT-NaPi2b Positive Population: Participants in the ITT analysis set with a NaPi2b expression value at or above the positive NaPi2b threshold of 75[a] and who received at least 1 dose of upifitamab rilsodotin at a starting dose of 36 mg/m^2 q4w (capped at a BSA of 2.2 m^2)
Secondary Endpoints	
Confirmed investigator-assessed ORR in the entire ITT population; Confirmed ORR by Independent Radiologic Review (IRR) in the ITT-NaPi2b Positive and in the ITT population; Investigator-assessed Duration of Response (DOR) in the ITT-NaPi2b positive population (DOR by IRR in the ITT-NaPi2b positive population is supplementary)	Intent-to-Treat (ITT) Population: Participants enrolled and received at least 1 dose of UpRi at starting dose of 36 mg/m^2 q4w (capped at a BSA of 2.2 m2)
Incidence and severity of adverse events	Safety Population: The analysis set of Participants who received any amount of upifitamab rilsodotin regardless of their starting dose

Abbreviations: BOR=best overall response; BSA=body surface area; DES=Dose Escalation; EXP=Expansion; HGSOC=high-grade serous ovarian cancer; ITT=intent-to-treat; NaPi2b=type II sodium dependent phosphate transporter (*SLC34A2*); TPS=total proportion score.

Error! Reference source not found. The TPS cut off was determined based on Cohort 1 (DES) and 2 (EXP) of MER-XMT-1532-1 and established prior to testing samples for UPLIFT.

Number of Patients Planned and Analyzed:

As of 31 May 2023, the data cut-off date used for these results, 93% and 95% of participants in the ITT-NaPi2b Positive and ITT populations have discontinued study treatment, and 53% and 55% have discontinued the study (Table 1). In the ITT Population, the most common reason for study treatment discontinuation was disease progression (63%, n=169) and the most common reason for study discontinuation was death (44%, n=119). Rates and reasons for discontinuation from study treatment and study were similar between the ITT-NaPi2b positive and ITT populations.

Table 1: Summary of Patient Disposition by Populations

Category	ITT 36.0 mg/m^2 (N=268)[a]	ITT-NaPi2b Positive 36.0 mg/m^2 (N=141)[b]
Patients who discontinued study treatment	254 (94.8%)	131 (92.9%)
Disease progression[c]	169 (63.1%)	90 (63.8%)
Radiographic - soft tissue	152 (56.7%)	79 (56.0%)
Radiographic - bone	6 (2.2%)	5 (3.5%)
Category	**ITT 36.0 mg/m^2 (N=268)[a]**	**ITT-NaPi2b Positive 36.0 mg/m^2 (N=141)[b]**

Clinical - CA125	24 (9.0%)	12 (8.5%)
Clinical - other tumor marker	1 (0.4%)	0
Clinical - other	21 (7.8%)	13 (9.2%)
AE/toxicity	64 (23.9%)	25 (17.7%)
Death	4 (1.5%)	3 (2.1%)
Physician decision	6 (2.2%)	5 (3.5%)
Withdrawal by patient	11 (4.1%)	8 (5.7%)
Patients who discontinued study	**148 (55.2%)**	**74 (52.5%)**
Death	119 (44.4%)	57 (40.4%)
Lost to follow-up	4 (1.5%)	3 (2.1%)
Withdrawal of consent by patient	16 (6.0%)	10 (7.1%)
Study terminated by sponsor	0	0
Physician decision	9 (3.4%)	4 (2.8%)

Abbreviations: AE=adverse event; CA125=cancer antigen 125; ITT=Intent-to-Treat; NaPi2b=type II sodium dependent phosphate transporter *(SLC34A2)*.

[a] Percentages are based on the ITT Population.

[b] Percentages are based on the ITT-NaPi2b Positive Population.

Error! Reference source not found. Percentages are based on the SAF.

[c] Patients may be counted in more than one disease progression type.

Source: Table 14.1.1

Diagnosis and Main Criteria for Inclusion:

The study enrolled adult participants with platinum resistant HGSOC, including cancers of ovarian, fallopian tube, or primary peritoneal origin. Participants must have had measurable disease by Response Evaluable Criteria in Solid Tumors (RECIST) version 1.1 and an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

General inclusion and exclusion criteria are described in the protocol, and cohort-specific inclusion and exclusion criteria is as follows.

HGSOC-specific Inclusion Criteria (Cohort 3)

1. Participants must have had a histological diagnosis of HGSOC, which included fallopian tube and primary peritoneal cancer that was metastatic or recurrent.
2. Platinum-resistant disease, as defined:
    a. Participants who had received only 1 line of platinum-based therapy must have received at least 4 cycles of platinum-containing chemotherapy, had a response (CR or PR), and have progressed between 3 months and ≤6 months after the date of the last dose of platinum-based therapy.
    b. Participants who had received 2 to 4 prior lines of platinum-based therapy must have received at least 4 cycles of platinum-containing chemotherapy within their last platinum-based regimen and then progressed within 6 months after the date of the last dose of platinum.
3. One to 4 prior lines of systemic therapy for ovarian cancer:
    a. Participants who had received 1 to 2 prior lines of systemic therapy must have received prior treatment with bevacizumab.

b. In France, participants must have received at least 2 lines of systemic therapy and were not candidates for surgery.

c. Definitions for prior lines of therapy:

i. Adjuvant ± neoadjuvant was considered 1 line of therapy as long as they were the same regimens (e.g., platinum/taxane for 4 cycles before surgery followed by platinum/taxane for 4 cycles after surgery).

ii. Maintenance therapy (e.g., bevacizumab, poly [ADP-ribose] polymerase inhibitor [PARPi], endocrine therapy) was considered as part of the preceding line of therapy (i.e., not counted independently).

iii. Therapy given for only 1 cycle and discontinued due to toxicity in the absence of progression was not counted as a new line of therapy; therapy given for 2 or more cycles was counted as a line of therapy. Substitutions of different platinum agents or taxanes were not counted as new lines.

iv. Hormonal therapy (e.g., tamoxifen, letrozole) was counted as a separate line of therapy unless it was given as maintenance.

d. In Sweden, participants must have received prior treatment with pegylated liposomal doxorubicin or paclitaxel, if not contraindicated.

e. In Finland, participants must have exhausted available curative, effective, or suitable treatment options for HGSOC (e.g., have received paclitaxel, pegylated doxorubicin or topotecan).

3. Participants must have provided an archived tumor tissue block or slides; if not available, undergo procedure to obtain a new tumor biopsy using a low-risk, medically routine procedure.

Investigational Product, Dosage, and Mode of Administration:

Upifitamab rilsodotin was administered intravenously via an antecubital or indwelling venous catheter. The initial dose for each participant was administered over 90 minutes. If no infusion-related reaction occurred, all subsequent doses could be administered over 30 to 90 minutes.

Demographics and Baseline Characteristics:

The demographic and baseline characteristics between the ITT-NaPi2b positive population and ITT Population were similar. The median age of participants in ITT Population was 61.5 years of age. Approximately 60% of participants were enrolled in Europe; the remainder were enrolled as indicated in the table below.

Approximately half of the participants (52.6%) in the ITT Population were NaPi2b positive (TPS ≥75). Four participants had a TPS not reported (1.5%) and were considered NaPi2b negative; these participants were not included in the Per Protocol Population.

Table 2: Demographic and Baseline Characteristics, ITT and ITT-NaPi2b Positive Populations

Category	ITT 36.0 mg/m^2 (N=268)	ITT-NaPi2b Positive 36.0 mg/m^2 (N=141)
Sex		

Female, n	268	141
Of childbearing potential	1 (0.4%)	0
Post-menopausal	112 (41.8%)	58 (41.1%)
Sterilized/otherwise not of childbearing potential	155 (57.8%)	83 (58.9%)
Age (years), n	268	141
Median	61.5	60.0
Age (years), n	268	141
18-<65 years	166 (61.9%)	94 (66.7%)
65-<75 years	81 (30.2%)	40 (28.4%)
≥75 years	21 (7.8%)	7 (5.0%)
≥65 years	102 (38.1%)	47 (33.3%)
Ethnicity, n	268	141
Hispanic or Latino	17 (6.3%)	4 (2.8%)
Not Hispanic or Latino	210 (78.4%)	116 (82.3%)
Not reported	41 (15.3%)	21 (14.9%)
Race, n	268	141
American Indian or Alaska Native	1 (0.4%)	1 (0.7%)
Asian	4 (1.5%)	2 (1.4%)
Black or African American	4 (1.5%)	4 (2.8%)
White	229 (85.4%)	122 (86.5%)
Other	2 (0.7%)	1 (0.7%)
Not reported	28 (10.4%)	11 (7.8%)
Geographic Region, n	268	141
North America	101 (37.7%)	50 (35.5%)
Europe	160 (59.7%)	87 (61.7%)
Asia Pacific	7 (2.6%)	4 (2.8%)
United States	95 (35.4%)	45 (31.9%)
Non-United States	173 (64.6%)	96 (68.1%)
Baseline BSA (m^2)[a], n	248	129
Median	1.740	1.740
Baseline ECOG performance status, n	268	141
0	154 (57.5%)	73 (51.8%)
1	114 (42.5%)	68 (48.2%)
Central NaPi2b expression TPS[b], n	268	141
Negative [TPS <75]	123 (45.9%)	0
Positive [TPS ≥75]	141 (52.6%)	141 (100.0%)
NE	4 (1.5%)	0

Abbreviations: BSA=body surface area; ECOG=Eastern Cooperative Oncology Group; ITT=Intent-to-Treat; max=maximum; min=minimum; NaPi2b=type II sodium dependent phosphate transporter *(SLC34A2)*; NE=not evaluable; sqrt=square root; StD=standard deviation; TPS=tumor proportion score.
Note: Percentages are based on the number of patients with a non-missing value for each summary.
[a] BSA is calculated using Mosteller formula: BSA (m^2)=sqrt [(height(cm) × weight(kg)) /3600].
[b] TPS is calculated as: [(percent membrane differential intensity at 1+) + (percent membrane differential intensity at 2+) + (percent membrane differential intensity at 3+)] and can range from 0 to 100.
Source: Table 14.1.2.1, Table 14.1.2.2

Baseline Disease Characteristics and Prior Ovarian Cancer Therapy:

Most participants in the ITT Population had Stage III cancer at the time of initial diagnosis (65.5%), and approximately 30% had Stage IV cancer at the time of initial diagnosis (29.6%). The median time since initial diagnosis for participants in the ITT Population was 35.38 months. Similar to the participants in the ITT population, most participants in the ITT-NaPi2b Positive Population had Stage III cancer at the

time of initial diagnosis (61.7%), and approximately 36% had Stage IV cancer at the time of initial diagnosis (35.5%). The median time since initial diagnosis for participants in the ITT-NaPi2b Positive Population was 32.88 months.

Per the study eligibility criteria, all participants had recurrent high-grade serous carcinoma and had received prior anti-cancer therapy. In the ITT Population, 83.6% of participants had received prior bevacizumab or bevacizumab biosimilars, and 68.7% had received prior PARPi. Approximately 42% of participants in the ITT Population had received 3 prior lines of anti-cancer therapy, and 31% had received 4 prior lines of therapy.

Rates in the ITT-NaPi2b Positive Population were similar, with 83.0% receiving prior bevacizumab or bevacizumab biosimilars, and 68.8% receiving prior PARPi. Approximately 33% of participants in the ITT-NaPi2b Positive Population had received 3 prior lines of anti-cancer therapy, and 34% had received 4 prior lines of therapy.

Table 2: Prior Ovarian Cancer Therapy, ITT and ITT-NaPi2b Positive Populations

Characteristic	ITT 36.0 mg/m^2 (N=268)	ITT-NaPi2b Positive 36.0 mg/m^2 (N=141)
Number of prior lines of therapy		
3	113 (42.2%)	47 (33.3%)
4	83 (31.0%)	48 (34.0%)
1-2	72 (26.9%)	46 (32.6%)
Patients who received prior bevacizumab or prior bevacizumab biosimilars	224 (83.6%)	117 (83.0%)
Patients who received prior PARPi	184 (68.7%)	97 (68.8%)
Number of lines of prior therapy in a platinum-resistant setting		
0	125 (46.6%)	66 (46.8%)
1	102 (38.1%)	53 (37.6%)
2	35 (13.1%)	17 (12.1%)
3	6 (2.2%)	5 (3.5%)
Most recent platinum-free interval[a], n	268	141
Median	3.48	3.52

Abbreviations: ITT=Intent-to-Treat; max=maximum; min=minimum; NaPi2b=type II sodium dependent phosphate transporter *(SLC34A2)*; PARPi=poly (ADP-ribose) polymerase inhibitor; StD=standard deviation.

[a] Most recent platinum-free interval (months) is calculated as: (date of disease progression following last platinum infusion in last line of platinum therapy - date of last platinum infusion in last line of platinum therapy + 1)/30.44

Source: Table 14.1.4.1, Table 14.1.4.2

Criteria for Evaluation
Efficacy:

The primary endpoint of Investigator-assessed ORR in participants in the ITT-NaPi2b Positive Population was 15.6% (95% confidence interval [CI]: 10.0%, 22.7%). There were 2 CRs and 20 PRs observed.

Table 3: Confirmed Investigator-assessed ORR, DCR, and BOR, ITT-NaPi2b Positive Population

Category	ITT 36.0 mg/m^2 (N=268)	ITT-NaPi2b Positive 36.0 mg/m^2 (N=141)
ORR	35 (13.1%)	22 (15.6%)
Two-sided 95% CI[a]	9.3%, 17.7%	10.0%, 22.7%
DCR	157 (58.6%)	93 (66.0%)
Two-sided 95% CI[a]	52.4%, 64.5%	57.5%, 73.7%
CR	3 (1.1%)	2 (1.4%)
PR	32 (11.9%)	20 (14.2%)

Abbreviations: BOR=best overall response; CI=confidence interval; CR=complete response; DCR=disease control rate; ITT=Intent-to-Treat; NaPi2b=type II sodium dependent phosphate transporter (*SLC34A2*); NE=not evaluable; ORR=objective response rate; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.
Note: Percentages are based on the number of patients in the ITT-NaPi2b Positive Population.
Note: ORR is determined by Investigator radiologic review and is defined as the proportion of patients who achieve a confirmed PR or CR per RECIST v1.1.
Note: DCR is defined as the proportion of patients who achieve a confirmed CR, confirmed PR, or SD of any duration per RECIST v1.1 as assessed by the Investigator radiologic review.
[a] The exact 2-sided 95% CI is calculated based on the binomial distribution using the Clopper-Pearson method.
Source: Table 14.2.1.1, Table 14.2.7.1, Table 14.2.2.1, Table 14.2.8.1.1

Criteria for Evaluation
Safety:

The Safety Population was comprised of participants who received any amount of upifitamab rilsodotin, regardless of the starting dose. As a result, participants who received a 43.0 mg/m^2 dose of upifitamab rilsodotin are reflected in the Safety tables.

Overall Adverse Events

In the Safety Population (n=300), 99.7% of participants experienced at least 1 TEAE and most participants (97.3%) experienced treatment-related TEAEs during the study. Treatment-related TEAEs of Grade ≥3 were experienced by 76.3% of participants. There were 17 participants (5.7%) who experienced a TEAE leading to death at either dose level. The TEAE incidences were generally similar across both dose levels, although numerically higher incidences of SAEs, TEAEs leading to dose delay/hold, and TEAEs leading to dose reduction were observed in participants at the 43.0 mg/m^2 upifitamab rilsodotin starting dose. The analysis is limited due to the small sample size of this level.

Table 4: Overall Summary of TEAEs, Safety Population

Participants with [n (%)]	XMT-1536 36.0 mg/m^2 (N=268)	XMT-1536 43.0 mg/m^2 (N=32)	Total (N=300)
Any TEAE	267 (99.6%)	32 (100.0%)	299 (99.7%)
Any treatment-related TEAE	261 (97.4%)	31 (96.9%)	292 (97.3%)
Any TEAE by worst grade			
Grade 1	4 (1.5%)	0	4 (1.3%)
Grade 2	24 (9.0%)	3 (9.4%)	27 (9.0%)
Grade 3	203 (75.7%)	24 (75.0%)	227 (75.7%)
Grade 4	21 (7.8%)	3 (9.4%)	24 (8.0%)
Grade 5	15 (5.6%)	2 (6.3%)	17 (5.7%)
Any treatment-related TEAE by worst grade			
Grade 1	12 (4.5%)	0	12 (4.0%)
Grade 2	47 (17.5%)	4 (12.5%)	51 (17.0%)
Grade 3	181 (67.5%)	26 (81.3%)	207 (69.0%)
Grade 4	14 (5.2%)	1 (3.1%)	15 (5.0%)
Grade 5	7 (2.6%)	0	7 (2.3%)
Any SAE	143 (53.4%)	21 (65.6%)	164 (54.7%)
Any treatment-related SAE	77 (28.7%)	12 (37.5%)	89 (29.7%)
Any AECI	101 (37.7%)	12 (37.5%)	113 (37.7%)
Any treatment-related AECI	93 (34.7%)	11 (34.4%)	104 (34.7%)
Any TEAE leading to study drug discontinuation	70 (26.1%)	8 (25.0%)	78 (26.0%)
Any treatment-related TEAE leading to study drug discontinuation	50 (18.7%)	6 (18.8%)	56 (18.7%)
Any TEAE leading to study drug interruption	12 (4.5%)	1 (3.1%)	13 (4.3%)
Any treatment-related TEAE leading to study drug interruption	9 (3.4%)	1 (3.1%)	10 (3.3%)
Any TEAE leading to dose delay/hold	110 (41.0%)	15 (46.9%)	125 (41.7%)
Any treatment-related TEAE leading to dose delay/hold	87 (32.5%)	14 (43.8%)	101 (33.7%)
Any TEAE leading to dose reduction	72 (26.9%)	13 (40.6%)	85 (28.3%)
Any treatment-related TEAE leading to dose reduction	67 (25.0%)	13 (40.6%)	80 (26.7%)
Any TEAE leading to death	15 (5.6%)	2 (6.3%)	17 (5.7%)
Any treatment-related TEAE leading to death	7 (2.6%)	0	7 (2.3%)

Abbreviations: AE=adverse event; AECI=adverse event of clinical interest; SAE=serious adverse event; SAF=Safety Analysis Set; TEAE=treatment-emergent adverse event.
Note: Percentages are based on the number of patients in the SAF in each dose level and overall.
Note: AEs with an onset/worsening on or after start of study drug and within 60 days of the last dose of study drug are defined as TEAEs.
Note: AEs with a missing relationship to study treatment are considered related.
Note: AEs with missing severity grade are left as missing.
Source: Table 14.3.1.1

All-cause Mortality (Deaths Due to TEAEs)

TEAEs leading to death were reported in 5.7% of participants (n=17) participants in the Safety Population; the incidences were similar across both starting dose levels. Sepsis was reported in 4 participants and haemorrhage intracranial in 3 participants. All other TEAEs leading to death were reported in 1 participant each.

Table 5: TEAEs Leading to Death by SOC and PT, Safety Population

Participants with [n (%)]	XMT-1536 36.0 mg/m^2 (N=268)	XMT-1536 43.0 mg/m^2 (N=32)	Total (N=300)
Any TEAE leading to death	15 (5.6%)	2 (6.3%)	17 (5.7%)
Infections and infestations	3 (1.1%)	1 (3.1%)	4 (1.3%)
Sepsis	3 (1.1%)	1 (3.1%)	4 (1.3%)
Nervous system disorders	3 (1.1%)	1 (3.1%)	4 (1.3%)
Haemorrhage intracranial	3 (1.1%)	0	3 (1.0%)
Cerebrovascular accident	0	1 (3.1%)	1 (0.3%)
General disorders and administration site conditions	2 (0.7%)	0	2 (0.7%)
Death	1 (0.4%)	0	1 (0.3%)
Sudden death	1 (0.4%)	0	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.7%)	0	2 (0.7%)
Lymphangiosis carcinomatosa	1 (0.4%)	0	1 (0.3%)
Tumour haemorrhage	1 (0.4%)	0	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	2 (0.7%)	0	2 (0.7%)
Acute pulmonary oedema	1 (0.4%)	0	1 (0.3%)
Pulmonary haemorrhage	1 (0.4%)	0	1 (0.3%)
Cardiac disorders	1 (0.4%)	0	1 (0.3%)
Acute myocardial infarction	1 (0.4%)	0	1 (0.3%)
Gastrointestinal disorders	1 (0.4%)	0	1 (0.3%)
Peritoneal perforation	1 (0.4%)	0	1 (0.3%)
Vascular disorders	1 (0.4%)	0	1 (0.3%)
Shock	1 (0.4%)	0	1 (0.3%)

Abbreviations: AE=adverse event; PT=Preferred Term; SAF=Safety Analysis Set; SOC=System Organ Class; TEAE=treatment-emergent adverse event.
Note: Percentages are based on the number of patients in the SAF in each dose level and overall.
Note: AEs with an onset/worsening on or after start of study drug and within 60 days of the last dose of study drug are defined as TEAEs.
Note: AEs are coded by SOC and PT using MedDRA version 25.0. AEs are displayed in descending order of frequency of SOC and descending frequency of PT within each SOC based on the 36.0 mg/m^2 q4wk dose level. A patient reporting multiple cases of the same TEAE is counted once within each SOC and similarly counted once within each PT at the maximum severity.
Source: Table 14.3.1.10.1

Serious Adverse Events:

Overall, 54.7% of participants in the Safety Population experienced at least 1 SAE (Table 6). The most frequently reported SAEs (>10 participants) were pyrexia (6.7%), small bowel obstruction (5.3%), and abdominal pain (3.7%). The incidence of SAEs was numerically higher in participants who received an upifitamab rilsodotin 43.0 mg/m^2 starting dose than in participants who received an upifitamab rilsodotin 36.0 mg/m^2 starting dose, driven by higher incidences of SAEs in the PTs of dyspnoea, pneumonitis, sepsis, and small intestinal obstruction.

At least 1 treatment-related SAE was observed in 29.7% of participants (n=89) with 24.0% of participants experiencing an event of Grade ≥3 maximum severity. Grade 5 treatment-related SAEs occurred in 2.3% of participants (n=7; 3 haemorrhage intracranial and 1 each of the following: sepsis, shock, acute pulmonary oedema, and tumour haemorrhage).

At the 36.0 mg/m^2 upifitamab rilsodotin starting dose, treatment-related SAEs were observed in 28.7% (n=77) of participants. Treatment-related SAEs were observed in 37.5% (n=12) of participants at the 43.0 mg/m^2 upifitamab rilsodotin starting dose. In both groups of participants, most treatment-related SAEs were Grade 3: 18.3% (n=49) of participants at the 36.0 mg/m^2 starting dose and 25.0% (n=8) of participants at the 43.0 mg/m^2 upifitamab rilsodotin starting dose had at a treatment-related SAE with a maximum Grade 3 severity.

The incidence of Grade ≥3 treatment-related SAEs of pneumonitis was 6.3% (n=2) in participants at the 43.0 mg/m^2 upifitamab rilsodotin starting dose vs 1.1% (n=3) in participants at the 36.0 mg/m^2 starting dose. The analysis is limited due to the small sample size of the 43.0 mg/m^2 upifitamab rilsodotin starting dose level.

Table 6: SAEs by PT (≥2% Participants Total), SAF

Participants with [n (%)]	XMT-1536 36.0 mg/m^2 (N=268)	XMT-1536 43.0 mg/m^2 (N=32)	Total (N=300)
Any SAE	143 (53.4%)	21 (65.6%)	164 (54.7%)
Pyrexia	19 (7.1%)	1 (3.1%)	20 (6.7%)
Small intestinal obstruction	12 (4.5%)	4 (12.5%)	16 (5.3%)
Abdominal pain	11 (4.1%)	0	11 (3.7%)
Pleural effusion	7 (2.6%)	1 (3.1%)	8 (2.7%)
Sepsis	5 (1.9%)	3 (9.4%)	8 (2.7%)
Vomiting	7 (2.6%)	1 (3.1%)	8 (2.7%)
Fatigue	7 (2.6%)	0	7 (2.3%)
Intestinal obstruction	7 (2.6%)	0	7 (2.3%)
Pneumonitis	5 (1.9%)	2 (6.3%)	7 (2.3%)
Anaemia	5 (1.9%)	1 (3.1%)	6 (2.0%)
Ascites	6 (2.2%)	0	6 (2.0%)
Dyspnoea	3 (1.1%)	3 (9.4%)	6 (2.0%)

Abbreviations: AE=adverse event; PT=Preferred Term; SAE=serious adverse event; SAF=Safety Analysis Set; TEAE=treatment-emergent adverse event.
Note: Percentages are based on the number of patients in the SAF in each dose level and overall.
Note: AEs with an onset/worsening on or after start of study drug and within 60 days of the last dose of study drug are defined as TEAEs.
Note: AEs are coded by SOC and PT using MedDRA version 25.0. AEs are displayed in descending order of frequency of SOC and descending frequency of PT within each SOC based on the 36.0 mg/m^2 q4wk dose level. A patient reporting multiple cases of the same TEAE is counted once within each SOC and similarly counted once within each PT.
Source: Table 14.3.1.4.1

Treatment-emergent Adverse Events

Overall, 99.7% of participants in the Safety Population (n=300) experienced at least 1 TEAE; the incidences were similar across both starting dose levels. The most frequently reported TEAEs (≥40% of participants) were aspartate aminotransferase increased (71.7%; n=215), nausea (59.3%; n=178), fatigue (49.3%; n=148), anaemia (48.0%; n=144), and pyrexia (46.7%; n=140).

Several common PTs were observed at higher incidences in participants at the 43.0 mg/m^2 upifitamab rilsodotin starting dose compared to participants at the 36.0 mg/m^2 upifitamab rilsodotin starting dose (>10% difference): abdominal pain, blood alkaline phosphatase increased, chills, cough, decreased appetite, fatigue, hypomagnesaemia, and pneumonitis.

Higher incidences (>10% difference) of asthenia, blood lactate dehydrogenase increased, and constipation were observed in participants at the 36.0 mg/m^2 upifitamab rilsodotin starting dose compared to the 43.0 mg/m^2 starting dose.

Table 7: TEAEs by SOC and PT (PTs in ≥10% of Participants Total), Safety Population

Participants with [n (%)]	XMT-1536 36.0 mg/m^2 (N=268)	XMT-1536 43.0 mg/m^2 (N=32)	Total (N=300)
Any TEAE	267 (99.6%)	32 (100.0%)	299 (99.7%)
Gastrointestinal disorders	239 (89.2%)	29 (90.6%)	268 (89.3%)
Nausea	158 (59.0%)	20 (62.5%)	178 (59.3%)
Diarrhoea	90 (33.6%)	12 (37.5%)	102 (34.0%)
Constipation	88 (32.8%)	7 (21.9%)	95 (31.7%)
Vomiting	85 (31.7%)	11 (34.4%)	96 (32.0%)
Abdominal pain	82 (30.6%)	17 (53.1%)	99 (33.0%)
Abdominal distension	29 (10.8%)	4 (12.5%)	33 (11.0%)
Ascites	29 (10.8%)	1 (3.1%)	30 (10.0%)
General disorders and administration site conditions	238 (88.8%)	29 (90.6%)	267 (89.0%)
Pyrexia	127 (47.4%)	13 (40.6%)	140 (46.7%)
Fatigue	125 (46.6%)	23 (71.9%)	148 (49.3%)
Asthenia	80 (29.9%)	2 (6.3%)	82 (27.3%)
Oedema peripheral	32 (11.9%)	5 (15.6%)	37 (12.3%)
Chills	23 (8.6%)	8 (25.0%)	31 (10.3%)
Investigations	220 (82.1%)	26 (81.3%)	246 (82.0%)
Aspartate aminotransferase increased	191 (71.3%)	24 (75.0%)	215 (71.7%)
Alanine aminotransferase increased	92 (34.3%)	13 (40.6%)	105 (35.0%)
Blood lactate dehydrogenase increased	87 (32.5%)	6 (18.8%)	93 (31.0%)
Blood alkaline phosphatase increased	80 (29.9%)	17 (53.1%)	97 (32.3%)
Platelet count decreased	74 (27.6%)	12 (37.5%)	86 (28.7%)
Blood creatinine increased	36 (13.4%)	4 (12.5%)	40 (13.3%)
Metabolism and nutrition disorders	167 (62.3%)	23 (71.9%)	190 (63.3%)
Decreased appetite	89 (33.2%)	18 (56.3%)	107 (35.7%)
Hyponatraemia	49 (18.3%)	9 (28.1%)	58 (19.3%)
Hypokalaemia	42 (15.7%)	7 (21.9%)	49 (16.3%)
Hypomagnesaemia	39 (14.6%)	9 (28.1%)	48 (16.0%)
Hypoalbuminaemia	38 (14.2%)	3 (9.4%)	41 (13.7%)
Blood and lymphatic system disorders	164 (61.2%)	18 (56.3%)	182 (60.7%)
Anaemia	126 (47.0%)	18 (56.3%)	144 (48.0%)
Thrombocytopenia	70 (26.1%)	7 (21.9%)	77 (25.7%)
Respiratory, thoracic and mediastinal disorders	135 (50.4%)	23 (71.9%)	158 (52.7%)
Dyspnoea	62 (23.1%)	7 (21.9%)	69 (23.0%)
Cough	46 (17.2%)	10 (31.3%)	56 (18.7%)
Epistaxis	35 (13.1%)	7 (21.9%)	42 (14.0%)
Pneumonitis	29 (10.8%)	7 (21.9%)	36 (12.0%)
Nervous system disorders	123 (45.9%)	19 (59.4%)	142 (47.3%)
Headache	80 (29.9%)	12 (37.5%)	92 (30.7%)
Renal and urinary disorders	116 (43.3%)	17 (53.1%)	133 (44.3%)
Proteinuria	90 (33.6%)	11 (34.4%)	101 (33.7%)
Musculoskeletal and connective tissue disorders	115 (42.9%)	11 (34.4%)	126 (42.0%)
Arthralgia	49 (18.3%)	3 (9.4%)	52 (17.3%)
Myalgia	35 (13.1%)	3 (9.4%)	38 (12.7%)

Participants with [n (%)]	XMT-1536 36.0 mg/m^2 (N=268)	XMT-1536 43.0 mg/m^2 (N=32)	Total (N=300)
Back pain	28 (10.4%)	3 (9.4%)	31 (10.3%)
Vascular disorders	72 (26.9%)	4 (12.5%)	76 (25.3%)
Hypertension	42 (15.7%)	4 (12.5%)	46 (15.3%)

Abbreviations: AE=adverse event; PT=Preferred Term; SAF=Safety Analysis Set; SOC=System Organ Class; TEAE=treatment-emergent adverse event.
Note: Percentages are based on the number of patients in the SAF in each dose level and overall.
Note: AEs with an onset/worsening on or after start of study drug and within 60 days of the last dose of study drug are defined as TEAEs.
Note: AEs are coded by SOC and PT using MedDRA version 25.0. AEs are displayed in descending order of frequency of SOC and descending frequency of PT within each SOC based on the 36.0 mg/m^2 q4wk dose level. A patient reporting multiple cases of the same TEAE is counted once within each SOC and similarly counted once within each PT.
Source: Table 14.3.1.2.1

Conclusion:

The UPLIFT pivotal cohort in study MER-XMT-1536-1 did not meet its primary endpoint of investigator-assessed ORR in the NaPi2b-positive population (defined by a tumor proportion score (TPS) of ≥75%). Following the primary analysis of the UPLIFT Cohort, Mersana made the decision to terminate the XMT-1536 clinical development program.